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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,314	10/24/2005	Anthony Rosenzweig	00786/431002	9779

21559 7590 04/19/2007

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,314	ROSENZWEIG ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *15,16,20,21,29,30,42,45-49,51,54 and 55* is/are pending in the application.

4a) Of the above claim(s) *15,16,20,21,30,42,45-49,51,54 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01/31/2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 1-14, 17-19, 22-28, 31-41, 43, 44, 50, 52, 53, and 56-64 have been cancelled. Claims 15, 16, 20, 21, 30, 42, 45, 46-49, 51, 54, and 55 have been withdrawn. Claim 29 has been amended.

Claim 29 is under examination.

Specification

2. The claim listing is objected to because the claim listing does not indicate the correct status of claims 49 and 51. It is noted that claims 49 and 51 have been withdrawn; however, they are listed as "original". Appropriate correction is required.

Response to Arguments

Specification

3. The objection to the specification is withdrawn in response to Applicant's arguments filed on 01/31/2007.

Drawings

3. The objection to the drawings because Fig. 8D, 9A, and 12C were not of sufficient quality is withdrawn in response to Applicant's submission of replacement drawings on 01/31/2007.

Claim Rejections - 35 USC § 101

4. Claim 29 remains rejected under 35 U.S.C. 101 for being directed to non-statutory subject matter, for the reasons of record set forth in the prior Office action. Applicant's arguments filed on 01/31/2007 have been considered but are not found persuasive.

Applicant submits that the amendment to the claim to recite recombinant dominant negative FADD obviates the rejection. However, it is noted that recombination can naturally occur and therefore a cell comprising a recombinant dominant negative FADD is still to a product of nature, i.e., a cell in which a naturally recombination process has occurred. The amendment to the claim should clearly indicate that such a cell is not a result of a naturally occurring recombination process to obviate this rejection.

Claim Rejections - 35 USC § 103

5. Claim 29 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Seino et al. (Annals of Surgery, 2001, 234: 681-688), in view of Heinke et al. (Cardiovascular Research, 2001, 49: 127-134) for the reasons of record set forth in the prior Office action mailed on 07/28/2006. Applicant's arguments filed 01/31/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the cited references fail to teach all claim limitations and fail to provide a reasonable expectation of success.

Applicant argues that Seino et al. teach dominant negative FADD expression in the liver cells of a mouse after adenoviral transduction, wherein the expression of dominant negative FADD inhibits apoptosis without affecting NF-κB expression. Applicant argues that since Seino et al. do not teach expression of dominant negative FADD in tissues other than liver they do not teach the present invention, i.e., cardiomyocytes expressing recombinant dominant negative FADD. With respect to Heinke et al., Applicant argues that the reference teaches that FADD expression and apoptosis are increased in a canine model of heart failure and that, although the Examiner asserts that the reference teaches that overexpression of Fas, Fas-L, and FADD results in increased apoptosis in the canine model, Applicant did not find such disclosure in the reference. Applicant submits that Heinke et al. only observe a correlation between apoptosis and increased FADD expression without providing any evidence of causal relationship between the two and that Heinke et al. do not teach expression of dominant negative FADD in cardiomyocytes and do not indicate that apoptosis in the heart can be reduced by decreasing FADD expression by expressing dominant negative FADD. Applicant argues that, in the absence such indication, one of skill in the art would not conclude that reducing FADD expression in cardiomyocytes would diminish apoptosis, because FADD activity is dependent upon interaction with other proteins such as Fas, and therefore, expression changes do not indicate a corresponding effect on FADD activity directly or on its downstream effectors. Therefore, Applicant concludes that Heinke et al. also fail to teach the present invention. Applicant continues arguing that the combination of Seino et al. and Heinke et al. does not teach or suggest cardiomyocytes

expressing recombinant dominant negative FADD and that one of skill in the art would not have been expected to have a reasonable expectation of success in reducing apoptosis in cardiomyocytes by expressing dominant negative FADD. Applicant argues that the instant specification teaches that FADD activity is cell-specific and that the instant invention describes for the first time that FADD inhibits TNF-α-induced activation of NF-κB in cardiomyocytes, which is not true for other cell lines such as smooth muscle cells, and that HEK293 cells FADD alone, in the absence of TNF-α, was sufficient to induce NF-κB activation (specification, p. 33, lines 24 and 25) and therefore, FADD activity cannot be predicted in one cell type based on its activity in another cell type. Applicant continues arguing that, consistent with this observation, while TNF-α-induced activation of NF-κB in cardiomyocytes is reduced by dominant negative FADD (p. 36, lines 17-25), Seino et al. teach that TNF-α-induced activation of NF-κB in the liver is not reduced by the dominant negative FADD. Therefore, it is impossible to predict what effect FADD or dominant negative FADD expression would have in a particular cell type and for this reason Seino et al. do not provide a reasonable expectation of success and cannot be used to render obvious the present invention. Applicant submits that Heinke et al. do not rectify this unpredictability because both the model and the results described by them are problematic, since the model may not be applicable to most cardiac diseases and for these reasons one of skill in the art would not conclude that the results generated by Heinke et al. would apply to most cardiac diseases. Because the combination of Seino et al. and Heinke et al. cannot render the instant invention obvious, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however the rejection is maintained for the following reasons:

First, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Second, in response to Applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant's argument that FADD activity is cell specific and it would be impossible to predict what effect expression of FADD or dominant negative FADD would have in cardiomyocytes based on the results found in other cell types is not found persuasive. The art teaches that Fas and FADD are apoptosis inducers in all cell types. The fact that TNF-α-induced activation of NF-κB in cardiomyocytes is reduced by dominant negative FADD in cardiomyocytes (p. 36 and 37 of Applicant's specification) and not in liver cells (Seino et al., p. 682, column 1) is irrelevant because dominant negative FADD was able to reduce apoptosis in both cardiomyocytes (p. 3 of

Applicant's specification) and liver (Seino et al., p. 682, column 1, p. 687, column 1) irrespective of whether NF-κB activity was inhibited or not. Therefore, based on these results, one of skill in the art would not have concluded that FADD pro-apoptotic activity is cell-specific and would have realized that dominant negative FADD could be used to inhibit apoptosis regardless of whether NF-κB was inactivated or not. Seino et al. teach that cells express on their surface two receptors, TNF receptor (TNFR) and Fas, each capable of separately triggering apoptosis upon binding to distinct ligands (i.e., TNFα and Fas respectively), that TNFR and Fas activity is mediated by FADD recruited to the TNFR or Fas cytoplasmic domains, and that it is a known fact in the art that apoptosis mediated by both TNFR and Fas is inhibited by the blockade of FADD (Abstract, p. 681, column 2 bridging p. 682). Heinke et al. teach that cardiomyopathies in general are associated with a progressive loss of myocytes in humans via apoptosis and therefore, loss of cardiomyocyte by apoptosis is not restricted to their model (p. 127, column 2). Importantly, Heinke et al. teach induction of Fas and FADD in their paced animals, whereas Fas and FADD was not induced in the control animals (i.e., animals in which cardiomyocytes do not undergo enhanced apoptosis), i.e., the observed changes in FADD expression do indicate a corresponding effect on FADD activity and therefore on its downstream effectors (Abstract, p. 130, columns 1 and 2, Fig. 2, p. 131, column 2, Fig. 3 and 5, p. 132, columns 1 and 2, Fig. 7). Based on these teachings taken together, one of skill in the art would have readily recognized that the induction of FADD is responsible for apoptosis in cardiomyocytes and would reasonably conclude that FADD inhibition by using the dominant negative FADD would diminish apoptosis. The

argument that the model of Heinke et al. may not be applicable to most cardiac diseases and for these reasons one of skill in the art would not conclude that the results generated by Heinke et al. would apply to most cardiac diseases is only an argument not supported by any evidence. Heinke et al. clearly teach that cardiomyopathies in general are associated with a progressive loss of cardiomyocytes in humans via apoptosis. The important factor is that in cardiomyocytes are lost because of apoptosis. Therefore, one of skill in the art would have realized that FADD inhibitors could be used to inhibit apoptosis, regardless of the disease. Even assuming, for the sake of the argument that this would not be true, the desire to treat one disease (i.e., the one modeled by Heinke et al.) would have provided enough motivation for one of skill in the art to obtain cardiomyocytes expressing recombinant dominant negative FADD. Therefore, the combined references as a whole render the instant invention *prima facie* obvious.

6. Claim 29 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Chao et al. (J Biol Chem, August 30, 2002, 277: 31639-31645), for the reasons of record set forth in the prior Office action mailed on 07/28/2006.

Applicant provided an unsigned declaration under 37 C.F.R § 1.131 by Dr. Anthony Rosenzweig stating that Chao is not prior art because the reference represents Applicant's own work published less than one year before filing. However, the since the declaration is not signed by the Applicant, the rejection is maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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